UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,975	03/26/2004	Robert E. Davis	ACADIA.035A	7906

20995 7590 02/21/2008

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/809,975	DAVIS ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11 and 14-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 11/19/2007 amending claims 1 and adding new claims 14-18. Claims 5, 12-13 have been canceled. Newly submitted claims 14-18 will not be examined at this time because they are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly added claims are distinct because the compounds of formula (I) acquire a separate status in the art as they are classified in different classification (e.g. 514/302, 514/577, 540/600, 544/349, 546/115 etc). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 14-18 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Hence Claims 1-4, 6-11 are pending and are being examined on the merits herein. The elected species is free of prior art. Hence the search was expanded to include other species in claim 6 and the following rejections have been made.

Response to Remarks

The rejection of claims 1-4, 6-11 under 35 U.S.C. 103(a) as being unpatentable over Lavand'homme et al. (Anesthesiology, 1999, 91, 1455-61) in view of Skjaerback et al. (US 2003/0176418) and further in view of Mitchell (J of Pain and Symptom Management, Vol. 21, 5, May 2001) and rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Lavand'homme et al. (Anesthesiology, 1999, 91, 1455-61) in

view of Skjaerback et al. (US 2003/0176418) and further in view of Mitchell (J of Pain and Symptom Management, Vol. 21, 5, May 2001) as applied to claims 1-4, 6-11 above and further in view of Baker et al. (U.S. 5,242,927) are withdrawn due to the Applicants' statement in the response dated 11/19/2007 that Skjaerback et al. (US 2003/0176418) and the claimed invention was owned by the same assignee at the time of the claimed invention of made (103 (c)). Further search and consideration necessitated the following new rejections made in this office action. Hence the action is made non final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hyperalgesic and allodynia effects for compounds xanomeline, oxotremorine, milameline, formula VII, VIII and IX (Table 1 of specification) does not reasonably provide enablement for all other muscarinic agonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing

Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the Invention:

The rejected claims are drawn to a method for treating neuropathic pain without alleviating pain comprising providing the subject an effective amount of at least one compound that selectively activates the M(1) receptor subtype.

(2) Breadth of the claims:

The rejected claims are broad as they are drawn to a method for treating neuropathic pain without alleviating pain comprising providing the subject an effective amount of at least one compound that selectively activates the M(1) receptor subtype. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

(3) Guidance of the Specification:

The guidance given by the specification is for treating clinical components of neuropathic pain namely hyperalgesia and allodynia by compounds of formula VII, VIII and IX.

(4) Working Examples:

The specification provides examples for treating clinical components of neuropathic pain namely hyperalgesia and allodynia by compounds of formula VII, VIII and IX.

(5) The relative skill of those in the art:

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

(6) The predictability of art:

The rejected claims are drawn to a method for treating neuropathic pain without alleviating acute pain comprising providing the subject an effective amount of at least one compound that selectively activates the M(1) receptor subtype. The claims are very broad and there is a high degree of unpredictability involved. Applicants have stated in the specification that direct acting muscarinic receptor agonists also are antinociceptive in a variety of animal models of acute pain (Bartolini et al., 1992; Brodie and Proudfit, 1984; Capone et al., 1999; Hartvig et al., 1989; Pedigo et al, 1975; Przewlocka et al., 1999; Shannon et al., 1997; Sheardown et al., 1997) and these data further support the role for muscarinic receptor activation in the control of acute pain states. Hence it is not predictable that all muscarinic receptor agonists that selectively activate M(1) type treat neuropathic pain without alleviating acute pain. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

(7) The Quantity of Experimentation Necessary:

In order to practice the above claimed invention, one of skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human

treatment, an appropriate animal model system to initially test the compounds for specific selectivity for type 1 muscarinic agonists and further test the compounds for the treatment of neuropathic pain and further establish that those compounds do not alleviate acute pain. If unsuccessful, one of skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of comprising administering the compounds that selectively activates M(1) receptor subtype whereby one or more symptoms of neuropathic pain are reduced and wherein the compound does not alleviate acute pain. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lavand'homme et al. (Anesthesiology, 1999, 91, 1455-61) Andersson et al. (WO 01/83472, publication date 8 Nov 2001) and further in view of Mitchell (J of Pain and Symptom Management, Vol. 21, 5, May 2001).

Lavand'homme et al. teaches cholinergic agents such as bethanechol, a muscarinic agonist reduces mechanical allodynia (tactile allodynia) after nerve injury to animals and may be useful in the treatment of neuropathic pain (see Abstract, p 1459, lines 4-6). The reference teaches the administration and determination of whether bethanechol reduced allodynia in the subject.

The reference does not teach the elected species, compounds in claim 6 to selectively activate the M (1) receptor subtype.

Andersson et al. teaches the compound of formula (VII) as in claim 6 of the instant application (p 13, line 7, claim 17, p 70, line 8, abstract, p 1, lines 4-10) as muscarinic M1 and M4 subtype. The reference further teaches the compound in a method of treatment of pain (p 4, line 26, p8, line 2, claim 57, p 78).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a compound of formula (VII) for the treatment of neuropathic pain. The motivation to do so is taught by Lavand'homme et al. Lavand'homme et al teaches bethanechol, a muscarinic agonist to be useful in the treatment of allodynia and

in the treatment of neuropathic pain. One of ordinary skill in the art would have been motivated at the time of the invention to use a compound of formula (VII) in the treatment of neuropathic pain as this compound has been shown to be a muscarinic agonist by Andersson et al.and one can expect similar success or superior results in relieving neuropathic pain by using this compound instead of bethanechol.

Lavand'homme et al and Andersson et al. do not teach a method of treating a subject for hyperalgesia, or thermal hyperalgesia and also do not teach the neuropathic pain to be associated with one of the diseases listed in claim 4.

Mitchell teaches that allodynia and hyperalgesia are clinical components of neuropathic pain and neuropathic pain conditions include cancer, painful diabetic neuropathy etc. (p 443, col. 2, lines 1-3, p446, col. 1, lines 7-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat subjects with hyperalgesia with a muscarinic agonist compound such as listed in claim 6 (formula VII). The motivation to do so is because Lavand'homme et al teaches that muscarinic agonist is useful in the treatment of allodynia a clinical symptom of neuropathic pain. It would have been obvious to one of ordinary skill in the art at the time of the invention to use a muscarinic agonist as listed in claim 6 to treat hyperalgesia which is another clinical symptom of neuropathic pain. Also, it would have been obvious to one of ordinary skill in the art to treat painful conditions associated with cancer, diabetes etc as Mitchell teaches them as neuropathic pain conditions and Lavand'homme et al teaches the usefulness of muscarinic agonist in the treatment of neuropathic pain.

Claims 1-4, 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lavand'homme et al. (Anesthesiology, 1999, 91, 1455-61) Andersson et al. (US 2002/0037886, publication date Mar 28 2002) and further in view of Mitchell (J of Pain and Symptom Management, Vol. 21, 5, May 2001).

Lavand'homme et al. teaches cholinergic agents such as bethanechol, a muscarinic agonist reduces mechanical allodynia (tactile allodynia) after nerve injury to animals and may be useful in the treatment of neuropathic pain (see Abstract, p 1459, lines 4-6). The reference teaches the administration and determination of whether bethanechol reduced allodynia in the subject.

The reference does not teach the elected species, compounds in claim 6 to selectively activate the M (1) receptor subtype.

Andersson et al. teaches the compound of formula (VII) as in claim 6 of the instant application (para 234, example 93, claim 17) as muscarinic M1 and M4 subtype. The reference further teaches the compound in a method of treatment of pain (para 0028, 48, 303, claims 57, 72).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a compound of formula (VII) for the treatment of neuropathic pain. The motivation to do so is taught by Lavand'homme et al. Lavand'homme et al teaches bethanechol, a muscarinic agonist to be useful in the treatment of allodynia and in the treatment of neuropathic pain. One of ordinary skill in the art would have been motivated at the time of the invention to use a compound of formula (VII) in the treatment of neuropathic pain as this compound has been shown to be a muscarinic

agonist by Andersson et al.and one can expect similar success or superior results in relieving neuropathic pain by using this compound instead of bethanechol.

Lavand'homme et al and Andersson et al. do not teach a method of treating a subject for hyperalgesia, or thermal hyperalgesia and also do not teach the neuropathic pain to be associated with one of the diseases listed in claim 4.

Mitchell teaches that allodynia and hyperalgesia are clinical components of neuropathic pain and neuropathic pain conditions include cancer, painful diabetic neuropathy etc. (p 443, col. 2, lines 1-3, p446, col. 1, lines 7-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat subjects with hyperalgesia with a muscarinic agonist compound such as listed in claim 6 (formula VII). The motivation to do so is because Lavand'homme et al teaches that muscarinic agonist is useful in the treatment of allodynia a clinical symptom of neuropathic pain. It would have been obvious to one of ordinary skill in the art at the time of the invention to use a muscarinic agonist as listed in claim 6 to treat hyperalgesia which is another clinical symptom of neuropathic pain. Also, it would have been obvious to one of ordinary skill in the art to treat painful conditions associated with cancer, diabetes etc as Mitchell teaches them as neuropathic pain conditions and Lavand'homme et al teaches the usefulness of muscarinic agonist in the treatment of neuropathic pain.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

***